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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,418	10/15/2001	Stephane Bejanin	G-142US05.REG	7350

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EXAMINER	
SMITH, CAROLYN L	
ART UNIT	**PAPER NUMBER**
1631	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S/M

Office Action Summary	Application No.	Applicant(s)	
	09/978,418	BEJANIN ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-31* is/are pending in the application.

4a) Of the above claim(s) *19-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *14-31* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and remarks, filed 12/29/03, are acknowledged. Canceled claim 2, amended claims 15-21, and new claims 22-31 are acknowledged. Claims 19-31 are withdrawn as being drawn to a non-elected Group.

Applicant's arguments, filed 12/29/03, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 14-18 are herein under examination.

PATENTABLE UTILITY GUIDELINES

The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

Claims Rejected Under 35 U.S.C. § 101

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

The rejection of claims 14-18 is maintained under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by a specific, substantial, and credible utility or, in the alternative, a well-established utility.

This rejection is maintained and reiterated for reasons of record.

The critical limitation of claims 14-18 is the polypeptide sequence of the claimed polypeptide SEQ ID NO: 42. The claimed polypeptide is not supported by a specific asserted utility because the disclosed uses of this composition are not specific and are generally applicable to any cytogram polypeptide. The specification states that the polynucleotide sequences of secretory proteins encoded by cDNAs may be useful as a "valuable source of therapeutic agents" (page 1, lines 23-24), diagnostics (page 2, lines 9-10), and in the generation of antibodies (page 2, lines 22-23). The secretory proteins include signal peptides that control secretion (page 1, lines 25-26) and membrane-translocating sequences to direct intracellular import of a protein which might aid in gene therapy strategies (page 2, lines 1-3). The specification lists particular information and possible uses of cytogram (cytotoxic granule membrane) proteins as the claimed sequence (SEQ ID NO: 42) appears to be a splice variant of GMP-17 or NKG7 with GenBank accession number Q16617 (page 186, lines 1-9). The specification lists

examples of cytogram protein use including its role in promoting NK and CTL cytotoxicity (page186, lines 18-19) as well as possible uses in various compositions and methods (page 186, lines 16 through page 191, line 18). The specification summarized modern biotechnology generally but never connects the specifically elected sequence (SEQ ID NO: 42) to any particular or available utility. The above-mentioned list of desirable utility for the claimed sequence falls short of a readily available utility. These are non-specific uses that are applicable to cytogram polypeptides in general and not particular or specific to the polypeptide being claimed.

Further, the claimed polypeptide is not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, a protein could be obtained and could then be used in conducting research to functionally characterize the protein. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved, such as the cytogram encoded by SEQ ID NO: 42, does not define a "real world" context for use. Similarly, the other listed utilities and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to many such compounds.

Applicant should explicitly identify a specific, substantial, and credible utility for the claimed invention and establish a probative relation between any evidence of record and the originally disclosed properties of the claimed invention. Due to a lack of either art recognized or alleged well established utility, the instant invention has been rejected due to also lacking the required combination of a specific, substantial, and credible utility. Although it maybe credible that the polypeptide is involved in promoting NK and CTL cytotoxicity, the lack of a specific and substantial utility, as explained above, sufficiently supports this rejection.

It is noted that applicant has identified a sequence which is known in the prior art and which has a stated sequence similarity to the claimed sequence. On page 16, line 28, through page 18, line 15 of the specification, Applicants mention using Basic Local Alignment Search Tool (BLAST) and FASTDB to evaluate protein and nucleic acid sequence identities. For instance, in Table 1, SEQ ID NO: 42 is listed as a cytogram, a splice variant of GMP-17 (GenBank Accession Number Q16617, on page 186, lines 1-2). Absent factual evidence, one skilled in the art would have reason to doubt that sequence similarity alone would reasonably support the assertion that the biological activity of the claimed subject matter would be the same as that of the similar sequence. Furthermore, it is unclear whether the similar sequence identified in the prior art has actually been tested for the biological activity or whether this also is an asserted biological activity based upon sequence similarity to yet a different sequence. Note that it would have been well known in the art that sequence similarity does not reliably correlate to structural similarity and that structural similarity does not reliably result in similar or identical biological activities. For example, it would have been well known that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. In the absence of factual evidence characterizing the structural and functional components of the biomolecule, the effects of these changes are largely unpredictable as to which ones will have a significant effect and which ones will be silent mutations having no effect. Several publications document the unpredictability of the relationship between sequence, structure, and function, although it is acknowledged that certain specific sequences have been found to be conserved in biomolecules having related function following a significant amount of further research. See Lopez et al. (Molecular Biology, 32:881-891,1999); Attwood (Science, 290:471-473, 2000); Gerhold et al. (BioEssays, 18(12):973-981, 1996); Wells et al. (Journal of

Leukocyte Biology, 61(5):545-550, 1997); and Russell et al. (Journal of Molecular Biology, 244:332-350, 1994). However, this level of factual evidence is absent here.

Also, since the claimed invention is not supported by a specific, substantial, and credible utility or a well-established utility for the reasons set forth above (refer to 35 U.S.C. § 101 rejection), one skilled in the art would not know how to use the claimed invention.

Applicants state that because the claimed invention can be used in a fashion similar to known cytogram polypeptides is indicative of the polypeptide having a "well-established" utility. This statement is found unpersuasive as the assertion that the claimed polypeptide is a cytogram appears to be an assertion without factual support. Further evidence would be needed to confirm such an assertion. Applicants state the articles submitted by Examiner regarding unpredictability of relationship between sequence, structure, and function do not address polypeptides that are splice variants of known polypeptides. This statement is found unpersuasive as these articles are documenting the unpredictability found within these relationships as they apply broadly in the biological field. Applicants have not satisfactory supplied evidence supporting the sequence, structure, and function relationship exists between the claimed polypeptide and other known polypeptides. Sequence comparison, such as that stated by Wells et al., may be one of the preliminary tools used to make predictions of biological function and relationships among biopolymers; however, it does not always provide conclusive evidence to confirm that a biological function exists or that a polypeptide belongs to a specific family unless further data are provided. Applicants note that one of skill in the art would have no reason to believe that the biochemical activity of a protein exhibiting less than 100% sequence similarity to a known protein would not be the same, or similar to that known protein. Applicants point out in the Wells et al. reference that a

polypeptide exhibiting as little as 20% identity can share similar or identical biological activity. This illustrates the unpredictability of knowing whether there is a similar biological activity or not between biopolymers, which further documents the need for further data to confirm such an assertion. Applicants quote the Russell et al. reference which states "both the sequence and the structure of similar proteins can evolve beyond recognition even when function is conserved." This quote further documents unpredictability and why additional factual evidence is necessary to support the utility assertions made in the instant invention. Applicants submit that an antibody recognizing the claimed sequence is a specific utility. This submission appears to be a generic utility commonly found in the biotechnology. Applicants further cite the specification regarding an antibody that specifically binds to a cytogram can be used in the detection of CTL and NK activity in mammalian cell cultures. This statement appears to be an assertion without factual support as evidence supplying convincing confirmation regarding the cytogram assertion is still needed. Applicants state that 53 N-terminal amino acids of elected SEQ ID NO: 42 are identical to the first 53 amino acids of GMP-17, such that the claimed invention could be used to generate antibodies useful for identification of cells infiltrating into renal allografts or cells involved in GVHD. This is found unpersuasive as Applicants have not sufficiently shown that the 53 amino acid residue region found in both SEQ ID NO: 42 and GMP-17 is crucial in antibody recognition. Furthermore, Applicants have not sufficiently shown that the identical amino acid region among GMP-17 and the instant invention is considered a conserved region among cytogram polypeptides that could potentially document this region as being crucial in antibody recognition for the purpose of identifying cells infiltrating into renal allografts or cells involved in GVHD.

Claims Rejected Under U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF ENABLEMENT

The rejection of claims 14-18 is maintained under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed sequence.

This rejection is maintained and reiterated for reasons of record.

For a sequence putatively assigned a biological function, even if correct, does not appear to be defined as to what use it is to be applied to. The significance of the sequence is undefined, further rendering it indiscernible how someone of skill in the art would use such an entity.

Due to the large quantity of experimentation necessary to determine activity or property of the disclosed polypeptide such that it can be determined how to use the claimed sequence, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, and the breadth of the claims which fail to recite particular biological activities, the specification fails to teach the skilled artisan how to make and use the claimed invention.

Without further data or sound scientific reasoning, it appears speculative whether the polypeptide of SEQ ID NO: 42 is indeed a cytogram. Relying on predictions of biopolymer function based on relationships in sequence matches is unpredictable (see second to last paragraph of the 35 USC § 101 rejection). With this in mind, additional evidence is necessary in order to satisfy the current lack of enablement. Several options exist to overcome this lack of enablement issue, such as supplying additional data or other scientific reasoning that would lead one of ordinary skill in the art to be able to make and/or use the present invention.

Applicants state that because experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. Applicants state the test of enablement is not whether any experimentation is needed, but whether it is undue. This is acknowledged; however, a significant amount of undue experimentation appears to be necessary in order to provide factual support to the assertion that the instant invention is within the cytogram family so that it can potentially be used in identifying activated cells involved in graft rejection and/or GVHD.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

March 3, 2004

ARDIN H. MARSCHEL
PRIMARY EXAMINER